

CLAIMS

We claim:

1. A targeting construct comprising:
 - (a) a first polynucleotide sequence homologous to an alpha-endosulfine gene;
 - (b) a second polynucleotide sequence homologous to the alpha-endosulfine gene;and
 - (c) a selectable marker.
2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.
3. A method of producing a targeting construct, the method comprising:
 - (a) providing a first polynucleotide sequence homologous to an alpha-endosulfine gene;
 - (b) providing a second polynucleotide sequence homologous to the alpha-endosulfine;
 - (c) providing a selectable marker; and
 - (d) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.
4. A method of producing a targeting construct, the method comprising:
 - (a) providing a polynucleotide comprising a first sequence homologous to a first region of the alpha-endosulfine gene and a second sequence homologous to the alpha-endosulfine gene; and
 - (b) inserting a positive selection marker in between the first and second sequences to form the targeting construct.
5. A cell comprising a disruption in an alpha-endosulfine gene.
6. The cell of claim 5, wherein the cell is a murine cell.
7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.
8. A non-human transgenic animal comprising a disruption in an alpha-endosulfine gene.
9. A cell derived from the non-human transgenic animal of claim 8.
10. A method of producing a transgenic mouse comprising a disruption in the alpha-endosulfine gene, the method comprising:

- (a) introducing the targeting construct of claim 1 into a cell;
 - (b) introducing the cell into a blastocyst;
 - (c) implanting the resulting blastocyst into a pseudopregnant mouse, and
 - (d) identifying the transgenic mouse comprising a disruption in the alpha-endosulfine gene.
11. A method of identifying an agent that modulates the expression or function of alpha-endosulfine, the method comprising:
 - (a) providing a non-human transgenic animal comprising a disruption in an alpha-endosulfine gene;
 - (b) administering an agent to the non-human transgenic animal; and
 - (c) determining whether the expression or function of alpha-endosulfine in the non-human transgenic animal is modulated.
 12. A method of identifying an agent that modulates the expression or function of alpha-endosulfine, the method comprising:
 - (a) providing a cell comprising a disruption in an alpha-endosulfine gene;
 - (b) contacting the cell with an agent; and
 - (c) determining whether expression or function of alpha-endosulfine is modulated.
 13. An agent identified by the method of claim 11 and claim 12.
 14. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits less body weight than wild-type mice
 15. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits improved glucose tolerance.
 16. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits blood glucose sensitivity to exogenous insulin.
 17. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits impaired glucose secretion while on a high fat diet.
 18. The non-human transgenic animal of claim 8, wherein the transgenic animal exhibits hyperactivity.
 19. A method of screening for biologically active agents, the method comprising:

(a) combining a putative agent with a mammalian alpha-endosulfine polypeptide; and

(b) detecting an effect of said agent on alpha-endosulfine activity; wherein detection of a decrease or an increase in alpha-endosulfine activity is indicative of a biologically active agent.

20. A method of screening for biologically active agents, the method comprising:

(a) combining a putative agent with an isolated cell comprising a nucleic acid encoding a mammalian alpha-endosulfine gene or a alpha-endosulfine promoter sequence operably linked to a reporter gene; and

(b) detecting an effect of said agent on alpha-endosulfine activity; wherein detection of a decrease or an increase in alpha-endosulfine activity is indicative of a biologically active agent

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